

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

40-330

APPLICATION NUMBER:

APPROVAL LETTER

ANDA 40-330

JUN 25 1999

Endo Pharmaceuticals, Inc.
Attention: Carol Patterson
500 Endo Blvd.
Garden City, NY 11530

Dear Madam:

This is in reference to your abbreviated new drug application dated August 24, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Oxycodone and Acetaminophen Tablets USP, 2.5 mg/325 mg and Oxycodone and Acetaminophen Tablets USP, 5 mg/325mg.

Reference is also made to your amendments dated October 6, 1998; April 20, April 26, May 6, May 14, June 11, and June 18, 1999.

We have completed the review of this abbreviated application and have concluded that the drugs are safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Oxycodone and Acetaminophen Tablets USP, 5 mg/325 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Percocet® Tablets, 5 mg/325 mg, of Endo Pharmaceuticals, Inc.). In addition, your Oxycodone and Acetaminophen Tablets USP, 2.5 mg/325 mg can be expected to have the same therapeutic effect as that of the reference listed drug product upon which the agency relied as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy, which you intend to use in your initial advertising or promotional campaigns. Please submit all

proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH
40-330**

APPLICATION NUMBER:

APPROVED DRAFT LABELING

Endo
ENDO LABORATORIES

PERCOCET®

(Oxycodone and Acetaminophen Tablets, USP) 

R_x only

DESCRIPTION



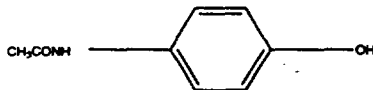
Each tablet, for oral administration, contains oxycodone hydrochloride and acetaminophen in the following strengths:

| | |
|-------------------------|---------|
| Oxycodone Hydrochloride | 2.5 mg* |
| Acetaminophen, USP | 325 mg |
| Oxycodone Hydrochloride | 5 mg* |
| Acetaminophen, USP | 325 mg |

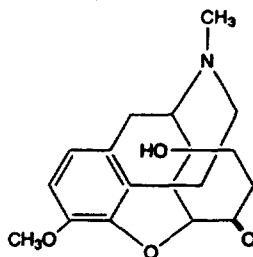
- * 2.5 mg oxycodone HCl is equivalent to 2.2409 mg of oxycodone.
5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.

Both strengths of PERCOCET also contain the following inactive ingredients: Colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, and stearic acid. In addition, the 2.5 mg/325 mg strength contains FD&C Red No. 40 Aluminum Lake and the 5 mg/325 mg strength contains FD&C Blue No. 1 Aluminum Lake.

Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. The molecular formula for acetaminophen is $C_8H_9NO_2$ and the molecular weight is 151.17. It may be represented by the following structural formula:



The oxycodone component is 14-hydroxydihydrocodeinone, a white, odorless, crystalline powder having a saline, bitter taste. The molecular formula for oxycodone hydrochloride is $C_{18}H_{21}NO_4 \cdot HCl$ and the molecular weight 351.83. It is derived from the opium alkaloid thebaine, and may be represented by the following structural formula:



CLINICAL PHARMACOLOGY

The principal ingredient, oxycodone, is a semisynthetic opioid analgesic with multiple actions qualitatively similar to those of morphine; the most prominent involves the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the oxycodone in PERCOCET are analgesia and sedation.

Oxycodone is similar to codeine and methadone in that it retains at least one-half of its analgesic activity when administered orally.

Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic.

2

INDICATIONS AND USAGE

PERCOCET (Oxycodone and Acetaminophen Tablets, USP) is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

PERCOCET should not be administered to patients who are hypersensitive to oxycodone, acetaminophen, or any other component of this product.

WARNINGS

Drug Dependence: Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral opioid-containing medications. Like other opioid-containing medications, PERCOCET is subject to the Federal Controlled Substances Act (Schedule II).

PRECAUTIONS

General

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of PERCOCET or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special Risk Patients: PERCOCET should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Information for Patients

Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET should be cautioned accordingly.

Drug Interactions

Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with oxycodone preparations may increase the effect of either the antidepressant or oxycodone.

The concurrent use of anticholinergics with opioids may produce paralytic ileus.

Usage in Pregnancy

Pregnancy Category C: Animal reproductive studies have not been conducted with PERCOCET. It is also not known whether PERCOCET can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. PERCOCET should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards.

Nonteratogenic Effects: Use of opioids during pregnancy may produce physical dependence in the neonate.

Labor and Delivery: As with all opioids, administration of PERCOCET to the mother shortly before delivery may result in some degree of respiratory depression in the newborn and the mother, especially if higher doses are used.

Nursing Mothers

It is not known whether PERCOCET is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PERCOCET is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus. At higher doses, oxycodone has most of the disadvantages of morphine including respiratory depression.

DRUG ABUSE AND DEPENDENCE

PERCOCET (Oxycodone and Acetaminophen Tablets, USP) is a Schedule II controlled substance.

Oxycodone can produce drug dependence and has the potential for being abused (See WARNINGS).

OVERDOSAGE

Acetaminophen

Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patient's estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural, or functional hepatic abnormalities.

Oxycodone

Signs and Symptoms: Serious overdosage with oxycodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to opioids, including oxycodone. Therefore, an appropriate dose of naloxone hydrochloride (usual initial adult dose 0.4 mg to 2 mg) should be administered preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitation (see package insert). Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under

4

continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION

Percocet 5 mg/325 mg

Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of opioids. PERCOCET (Oxycodone and Acetaminophen Tablets, USP) is given orally. The usual adult dosage is one tablet every 6 hours as needed for pain.

Percocet 2.5 mg/325 mg

PERCOCET Tablets (2.5 mg/325 mg) with half the oxycodone content (2.5 mg oxycodone) of PERCOCET Tablets 5 mg/325 mg are available for use when lower doses of oxycodone are desired. The recommended adult dosage is one or two tablets every six hours.

The total daily dose of acetaminophen should not exceed 4 grams.

HOW SUPPLIED

PERCOCET (Oxycodone and Acetaminophen Tablets, USP) are supplied as follows:

| | | |
|------------------------------|-------------------|------------------|
| 2.5 mg/325 mg | Bottles of 100 | NDC 63481-627-70 |
| Pink oval tablet | Bottles of 500 | NDC 63481-627-85 |
| embossed with | Unit dose package | NDC 63481-627-75 |
| "PERCOCET" on one | of 100 tablets | |
| side and "2.5" on the other. | | |

| | | |
|------------------------|-------------------|------------------|
| 5 mg/325 mg | Bottles of 100 | NDC 63481-623-70 |
| Blue, round, tablet, | Bottles of 500 | NDC 63481-623-85 |
| embossed with | Unit dose package | NDC 63481-623-75 |
| "PERCOCET" and "5" on | of 100 tablets | |
| one side and bisect on | | |
| the other. | | |

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

DEA Order Form Required.

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317



Manufactured by:
DuPont Pharma
Wilmington, Delaware 19880

PERCOCET® is a Registered Trademark of Endo Pharmaceuticals Inc.

Copyright © Endo Pharmaceuticals Inc. 1999

Printed in U.S.A.

6522-00/April, 1999



 **PERCOCET™** (Oxycodone and Acetaminophen Tablets, USP) 5 mg/325 mg



NEW
BLUE TABLET

Endo

ENDO LABORATORIES

PERCOCET™

(Oxycodone and
Acetaminophen Tablets, USP)

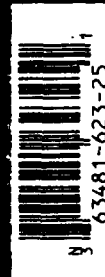
5 mg/325 mg



NDC 63481-623-25
NSN 6505-01-362-5340

R_x only

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317
By: DuPont Pharma
Wilmington, DE 19880



Each tablet contains:
Oxycodone Hydrochloride 5 mg*
Acetaminophen, USP 325 mg
*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.
DOSAGE: For dosage and full prescribing information, read
accompanying product information.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F).
25 TABLETS FOR HOSPITAL USE ONLY

48720C

NEW STRENGTH

NDC 63481-627-85

ENDO LABORATORIES

Endo **PERCOCET®** (Oxycodone and Acetaminophen Tablets, USP)

2.5 mg/325 mg

R_x only

Each tablet contains:
Oxycodone Hydrochloride . . . 2.5 mg*
Acetaminophen, USP 325 mg
*2.5 mg oxycodone HCl is equivalent to 2.2409 mg of oxycodone.

DOSAGE: For dosage and full prescribing information, read accompanying product information. Dispense in a tight, light-resistant container as defined in the USP. This is a bulk package and not intended for dispensing. Store at controlled room temperature 15°-30°C (59°-86°F).
DEA ORDER FORM REQUIRED.
500 TABLETS

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317
By: DuPont Pharma
Wilmington, DE 19880
70446/OD

63481-627-85

Multiple
Strengths:
2.5/325 or
5/325 mg. Do not
dispense unless
strength is
stated.

NDC 63481-623-75 NSN 6505-01-362-5340

NEW BLUE TABLET
ENDO LABORATORIES
PERCOCET®
(Oxycodone and Acetaminophen
Tablets, USP)
6 mg/325 mg

ENDO LABORATORIES
PERCOCET®
(Oxycodone and
Acetaminophen
Tablets, USP)
6 mg/325 mg

NDC 63481-623-75 NSN 6505-01-362-5340

NEW BLUE TABLET
ENDO LABORATORIES
PERCOCET®
(Oxycodone and Acetaminophen
Tablets, USP)
6 mg/325 mg

ENDO LABORATORIES
PERCOCET®
(Oxycodone and
Acetaminophen
Tablets, USP)
6 mg/325 mg

Each tablet contains:
Oxycodone Hydrochloride 5 mg* **R_x only**
Acetaminophen, USP 325 mg
*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.
DOSAGE: For dosage and full prescribing information, read
accompanying product information.
This unit-dose package is not child-resistant.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F).
100 TABLETS (Four 25-Tablet Blister Packs)
FOR HOSPITAL USE ONLY

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by:
DuPont Pharma
Wilmington, DE 19880

6747/OF

Each tablet contains:
Oxycodone Hydrochloride 5 mg* **R_x only**
Acetaminophen, USP 325 mg
*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.
DOSAGE: For dosage and full prescribing information, read
accompanying product information.
This unit-dose package is not child-resistant.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F).
100 TABLETS (Four 25-Tablet Blister Packs)
FOR HOSPITAL USE ONLY

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by:
DuPont Pharma
Wilmington, DE 19880



81%

Multiple Strengths:
2.5/325 or
5/325 mg. Do not
disperse unless
strength is
stated.

NDC 63481-627-75
ENDO LABORATORIES
PERCOCET®
(Oxycodone and Acetaminophen
Tablets, USP)
2.5 mg/325 mg

ENDO LABORATORIES
PERCOCET®
(Oxycodone and
Acetaminophen
Tablets, USP)
2.5 mg/325 mg

NDC 63481-627-75
ENDO LABORATORIES
PERCOCET®
(Oxycodone and Acetaminophen
Tablets, USP)
2.5 mg/325 mg

ENDO LABORATORIES
PERCOCET®
(Oxycodone and
Acetaminophen
Tablets, USP)
2.5 mg/325 mg

Each tablet contains:
Oxycodone Hydrochloride 2.5 mg* **R_x only**
Acetaminophen, USP 325 mg
*2.5 mg oxycodone HCl is equivalent to 2.2409 mg of oxycodone.
DOSAGE: For dosage and full prescribing information, read
accompanying product information.
This unit-dose package is not child-resistant.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F).
100 TABLETS (Four 25-Tablet Blister Packs)
FOR HOSPITAL USE ONLY

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by:
DuPont Pharma
Wilmington, DE 19880

Each tablet contains:
Oxycodone Hydrochloride 2.5 mg* **R_x only**
Acetaminophen, USP 325 mg
*2.5 mg oxycodone HCl is equivalent to 2.2409 mg of oxycodone.
DOSAGE: For dosage and full prescribing information, read
accompanying product information.
This unit-dose package is not child-resistant.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F).
100 TABLETS (Four 25-Tablet Blister Packs)
FOR HOSPITAL USE ONLY

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by:
DuPont Pharma
Wilmington, DE 19880

LOT:
EXP:



67%

ET40F



PERCOCET® (Oxycodone and Acetaminophen Tablets, USP) 5 mg/325 mg



41730F

NEW
BLUE TABLET

ENDO LABORATORIES

PERCOCET®

(Oxycodone and
Acetaminophen Tablets, USP)

5 mg/325 mg

Multiple
Strengths:
2.5/325
or 5/325 mg.
Do not dispense
unless strength
is stated.

NDC 63481-623-25
NSN 6505-01-362-5340

R_x only

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317
By: DuPont Pharma
Wilmington, DE 19880

63481-623-25

Each tablet contains:
Oxycodone Hydrochloride 5 mg*
Acetaminophen, USP 325 mg
*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.
DOSAGE: For dosage and full prescribing information, read
accompanying product information.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F).
25 TABLETS
FOR HOSPITAL USE ONLY.

| | | | |
|---|---|---|---|
| PERCOCET® Oxycodone HCl 2.5 mg Acetaminophen 325 mg Manufactured for Purdue Pharma L.P. Chadds Ford, PA 19017 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR | PERCOCET® Oxycodone HCl 2.5 mg Acetaminophen 325 mg Manufactured for Purdue Pharma L.P. Chadds Ford, PA 19017 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR | PERCOCET® Oxycodone HCl 2.5 mg Acetaminophen 325 mg Manufactured for Purdue Pharma L.P. Chadds Ford, PA 19017 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR | PERCOCET® Oxycodone HCl 2.5 mg Acetaminophen 325 mg Manufactured for Purdue Pharma L.P. Chadds Ford, PA 19017 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR |
|---|---|---|---|

PERCOCET® (Oxycodone and Acetaminophen Tablets, USP) 2.5 mg/325 mg 25 1999

| | | | |
|---|---|---|---|
| PERCOCET® Oxycodone HCl 2.5 mg Acetaminophen 325 mg Manufactured for Purdue Pharma L.P. Chadds Ford, PA 19017 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR | PERCOCET® Oxycodone HCl 2.5 mg Acetaminophen 325 mg Manufactured for Purdue Pharma L.P. Chadds Ford, PA 19017 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR | PERCOCET® Oxycodone HCl 2.5 mg Acetaminophen 325 mg Manufactured for Purdue Pharma L.P. Chadds Ford, PA 19017 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR | PERCOCET® Oxycodone HCl 2.5 mg Acetaminophen 325 mg Manufactured for Purdue Pharma L.P. Chadds Ford, PA 19017 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR |
|---|---|---|---|

Rx only

PERCOCET®
(Oxycodone and Acetaminophen Tablets, USP)

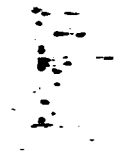
Each tablet contains:
Oxycodone Hydrochloride 2.5 mg
Acetaminophen, USP 325 mg
*2.5 mg oxycodone HCl is equivalent to 2.2408 mg of oxycodone.
DOSEAGE: For dosage and full prescribing information, read accompanying product information.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F).
28 TABLETS

2.5 mg/325 mg
NEW STRENGTH

NDC 63461-627-25

Manufactured by:
Purdue Pharma L.P.
Chadds Ford, PA 19017
U.S. Patent # 4,822,000

45834889/CP



**CENTER FOR DRUG EVALUATION AND
RESEARCH**

40-330

APPLICATION NUMBER:

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 40-330

DRUG PRODUCT: Oxycodone Hydrochloride
and Acetaminophen Tablets USP

FIRM: Endo
500 Endo Boulevard
Garden City, NY 11530

DOSAGE FORM: Tablet STRENGTH: 2.5 mg/325 mg
5.0 mg/325 mg

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP statement (p. 327) in original submission. Paragraph 306(k) certification submitted (p. 1052)

EIR acceptable for drug product manufacturer and drug substance manufacturer, 10/28/98.

Facilities included:

Alternate testing laboratory for release and stability testing of the finished product.

Endo Pharmaceuticals Inc.
500 Endo Blvd.
Garden City, NY 11530

The finished product will be manufactured, packaged (bottles), labeled and tested (release and stability, all packages) by third party contract laboratories.

Manufacturing, testing, packaging (bottles), and stability testing:

mpany

Packaging (Blister packaging), and labeling:

Drug Substance Manufacturers:

Acetaminophen USP (as Acetaminophen 90% Granulation -
Compap® L):

Greenville, S.C.

Oxycodone Hydrochloride USP

3ER for all facilities
acceptable 4/28/99
M. J. M.

BIO STUDY:

A change in strength for active ingredients approved per petition
by the Office of Generic Drugs, 5/26/98.

A waiver of in vivo bioequivalence study was granted by the
Division of Bioequivalence, L. Chuang, 11/5/98.

Dissolution testing results were found to be acceptable and the
firm's product was deemed bioequivalent to the reference product,
Percocet® Tablets, 5.0 mg/325 mg manufactured by Endo
Pharmaceuticals, by the Division of Bioequivalence, L. Chuang,
11/5/98.

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

All drug substances and drug product compendial.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN
CONTAINER SECTION?:

Stability for the following included:

| <u>Lot #</u> | <u>Batch Size</u> | <u>Sample</u> | <u>Test Conditions</u> |
|--------------|-------------------|---------------|------------------------|
| NC202 | - | 100's | 40°C/75% RH/3 months |
| | | 500's | 25°C/60% RH/12 months |
| | | Blister | |
| NC239 | | 100's | 40°C/75% RH/3 months |
| | | 500's | 25°C/60% RH/12 months |
| | | Blister | |

Container/Closure system:

100's in 150 cc, opaque white bottle, 38/400 cap,
75M innerseal/liner.

500's in 500 cc, opaque white bottle, 45/400
cap, 5M innerseal/liner.

Blister Packaging in PVC blister with foil backing, 25
blisters/sheet, 100 blisters per box.

All container/closure systems are as described in the
Container/Closure section.

Expiration date: 24 months based on accelerated stability data.

LABELING:

Description in package insert satisfactory for molecular
structure, molecular formula, formula weight, inactive
ingredients, product description and package size.

Professional labeling - satisfactory, A. Vezza,

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Biowaiver batches: Lot #NC202, stability data
included. Lot #NC239 tablets, stability data included.

DMF Acetaminophen USP (as Acetaminophen 90%,
satisfactory, S. Basaran, 1/27/99, no
amendments since then.

DMF dycodone Hydrochloride USP,
satisfactory, G.J.Smith, 2/26/99, no amendments since then.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY
MANUFACTURED VIA THE SAME PROCESS?):

See above.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS
BIO/STABILITY?:

Executed batch records for the 2.5 mg/325 mg
batch and the 5.0 mg/325 mg batch
(biowaiver/stability batches) included. Blank batch records were
submitted in the application for granulation and

compression for 2.5 mg/325 mg lets and
granulation and compression for 5.0 mg/325 tablets.
All scale-ups consistent with current Office policy: Proposed
manufacturing processes are the same as the bio/stability
batches.

CHEMIST:



DATE: 5/27/99

SUPERVISOR:



DATE: 5/27/99

RECORD OF TELEPHONE CONVERSATION

| | | | | | | |
|--|--|---------------------|-------------|-------------------|-------------|----------------|
| <p>Charlie Hoppes and I spoke to Carol Patterson today about ANDA 40-330. Charlie reiterated our discomfort with the fact that "Percocet" is going to be marketed in more than one strength. He requested that the 2.5 mg/325 mg tablet have "new strength" or "new tablet strength" on the container labels. Ms. Patterson wanted to know if they could use the labels they had currently and then make the change at the next printing. Charlie suggested a sticker to be attached to the container labels (to be attached to the unit dose carton as well) and Ms. Patterson agreed to this. She will be sending in correspondence committing to this as well as clarifying the information dissemination program to educate providers as to the new strength(s) of Percocet. Charlie also asked that (see USP) be added to the storage temperature recommendation throughout the labeling. Ms. Patterson agreed to this as well.</p> <p>Division of Labeling & Program Support</p> | DATE May 7, 1999 | | | | | |
| | ANDA NUMBER 40-330 | | | | | |
| | IND NUMBER | | | | | |
| | TELECON | | | | | |
| | <table border="0"> <tr> <td>INITIATED BY</td> <td>MADE</td> </tr> <tr> <td>APPLICANT/</td> <td>X BY</td> </tr> <tr> <td>SPONSOR</td> <td>TELE.</td> </tr> </table> | INITIATED BY | MADE | APPLICANT/ | X BY | SPONSOR |
| INITIATED BY | MADE | | | | | |
| APPLICANT/ | X BY | | | | | |
| SPONSOR | TELE. | | | | | |
| <table border="0"> <tr> <td>X FDA</td> <td>IN</td> </tr> <tr> <td></td> <td>PERSON</td> </tr> </table> | X FDA | IN | | PERSON | | |
| X FDA | IN | | | | | |
| | PERSON | | | | | |
| PRODUCT NAME PERCOCET | | | | | | |
| FIRM NAME ENDO | | | | | | |
| NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Carol Patterson Reg. Affairs | | | | | | |
| | TELEPHONE NUMBER (516) 522-3305 | | | | | |
| | SIGNATURE Adolph Vezza <i>Adolph Vezza 5/7/99</i> | | | | | |

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 40-330 Date of Submission: August 24, 1998

Applicant's Name: Endo Pharmaceuticals, Inc.

Established Name: Oxycodone and Acetaminophen Tablets USP,
2.5 mg/325 mg and 5 mg/325 mg

Labeling Deficiencies:

1. GENERAL COMMENTS:

We acknowledge that you will withdraw the brand name Percocet® from ANDA 85-106 if ANDA 40-330 is approved but we have the following concerns:

- a. Currently, the product Percocet® is available in only one strength (5 mg/325 mg) but if this ANDA is approved it will be available in two strengths. We further note that on page 802 of your submission that there are 4 different "Percocet®" strengths mentioned. We believe that this will result in medication errors particularly if an order for "Percocet®" with no strength associated with it is received. Please comment.
- b. How will providers be made aware of the fact that there is now a new Percocet® tablet strength?

2. CONTAINER 100s and 500s

Satisfactory, in draft.

3. UNIT DOSE BLISTER

Please include the established name, tablet strength, address, lot number and expiration date on each individual blister. Please note that without the strength on each individual blister, the 2.5 mg/325 mg strength will be indistinguishable from the 5 mg/325 mg strength (save for color).

4. UNIT DOSE CARTON 100s (4 x 25)

Include a statement as to whether or not the unit-dose package is child-resistant. If it is not child-resistant, include a statement if dispensed to outpatients, it should be with a child resistant container, for example:

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

[Note: The second sentence is optional.]

5. INSERT

a. GENERAL COMMENT

The requirements of 21 CFR 201.10(g)(1) must be met. The established name is to appear at least once in each column in association with the proprietary name.

b. DESCRIPTION

i. "FD&C Red No. 40 Aluminum Lake", "FD&C Blue No. 1 Aluminum Lake"

ii. Revise the third paragraph as follows:

Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a ... taste. It may be represented by the following structural formula [include the structural formula of acetaminophen here].

-iii. Include the molecular weight and molecular formula of both acetaminophen and oxycodone.

c. ~~OVER~~VERDOSAGE

Oxycodone, Treatment - Delete "Narcan®".

d. DOSAGE AND ADMINISTRATION

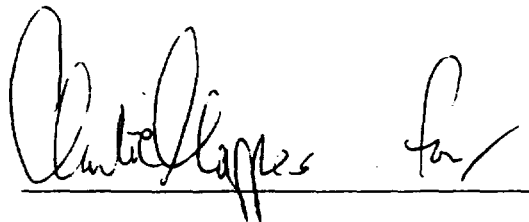
i. You have provided dosing for pediatric use of this product. Please disclose data sources to corroborate the appropriateness of the pediatric dosing schedules provided.

- ii. ... 6 to 12 years old ... (add "old")
- e. HOW SUPPLIED
 - i. Relocate the symbol "Rx only" to immediately below the title of the insert labeling.
 - ii. We note that you have indicated that the 5 mg/325 mg strength tablet is bisected but have made no indication that the 2.5 mg/325 mg tablet is also yet the DOSAGE AND ADMINISTRATION section for the 2.5 mg/325 mg strength tablet indicates "Children 12 years and older - One-half tablet every six hours." and "Children 6 to 12 years - One-quarter tablet every six hours." How will these doses be accurately measured unless the 2.5 mg/325 mg tablet is bisected (or quadrisected)?
 - iii. Add a space between "temperature" and "15°".
 - iv. Delete the reference to Narcan®.

Please revise your unit dose blister labels and unit dose carton and insert labeling, as instructed above, and submit in draft.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

| | |
|-----------------------------|---------------------------|
| Oxycodone HCl Acetaminophen | Endo Pharmaceuticals Inc. |
| Tablets, | Garden City, NY |
| 2.5 mg/325 mg & 5 mg/325 mg | Submission Date: |
| ANDA #40-330 | August 24, 1998 |
| Reviewer: Lin-Whei Chuang | |

Review of Waiver Requests and Dissolution Data

The test products will be branded as Percocet® 2.5 mg/325 mg tablets (pink) and 5 mg/325 mg tablets (blue). The reference listed drug is the firm's currently approved Percocet® 5 mg/325 mg white tablets (NDA#85-106).

The new strength (2.5 mg/325 mg, pink tablets) was found suitable for submission via suitability petition doc. #97P-0347/CP1 approved by the Agency on 5/26/98.

The 5 mg/325 mg blue tablet is a reformulation of the currently approved white tablet.

Formulations of the reference and test products are shown below in Table 1:

| Table 1: Formulations of Reference and Test products | | | |
|--|--|---|--|
| Ingredient | 5 mg/325 mg (reference - white tablet) | 2.5 mg/325 mg (test - pink tablet) | 5 mg/325 mg (test - blue tablet) |
| | mg/Tablet | | |
| Oxycodone HCl | 5 | 2.50 | 5.00 |
| Acetaminophen* | | | |
| Microcrystalline Cellulose | | | |
| Color | | | Blue |
| Croscarmellose Sodium | | | |
| Colloidal Silicone Dioxide | 11 | 12.18 | 12.18 |
| Stearic Acid | | | |
| Starch | | | |
| Povidone | | | |
| Sucrose | | | |
| Total Weight | 330 | --- | |

* = (in the form of Compap-L)

Comparative dissolution tests were conducted as shown in Table 2:

Table 2: Comparative Dissolution Tests

Drug: Oxycodone HCl / Acetaminophen Tablets
Dose Strength: 2.5 mg/325 mg (pink) & 5 mg/325 mg (blue)
ANDA No.: 40-330
Firm: Endo Pharmaceuticals Inc.
Submission Date: 8/24/98

I. Conditions for Dissolution Testing:

Method Ref.: USP 23
USP 23 Apparatus: 2 (Paddle) RPM: 50
Medium: 0.1N HCl Volume: 900 mL No. Units Tested: 12
Tolerance (Q): NLT in 45 min of both ingredients
Reference Drug: Percocet® 5 mg/325 mg white tablets (Endo)
Assay Method:

II. Results of In Vitro Dissolution/Release Testing:

| Sampling Times min | Test Product: Oxycodone HCl / Acetaminophen pink tablet Batch No.: NC202 Strength: 2.5/325 mg | | | Reference Product: Percocet® white tablet Lot No.: EMD226A Strength: 5/325 mg | | |
|-----------------------|---|---------|------|--|---------|------|
| | Mean % | Range % | % CV | Mean % | Range % | % CV |
| | Amount of Oxycodone HCl Dissolved | | | Amount of Oxycodone HCl Dissolved | | |
| 15 | 96.1 | | 2.2 | 92.3 | | 4.9 |
| 30 | 97.5 | | 1.8 | 98.7 | | 2.1 |
| 45 | 98.4 | | 1.6 | 99.7 | | 1.4 |
| 60 | 98.3 | | 1.4 | 100.6 | | 1.2 |
| | Amount of Acetaminophen Dissolved | | | Amount of Acetaminophen Dissolved | | |
| 15 | 96.4 | | 2.7 | 64.2 | | 3.9 |
| 30 | 98.1 | | 1.4 | 78.3 | | 9.9 |
| 45 | 98.8 | | 1.2 | 82.7 | | 9.9 |
| 60 | 99.2 | | 1.3 | 84.9 | | 9.1 |
| Sampling Times min | Test Product: Oxycodone HCl Acetaminophen blue tablet Batch No.: NC239 Strength: 5/325 mg | | | | | |
| | Mean % | Range % | % CV | | | |
| | Amount of Oxycodone HCl Dissolved | | | | | |
| 15 | 94.7 | | 7.4 | | | |
| 30 | 98.1 | | 2.2 | | | |
| 45 | 98.8 | | 1.5 | | | |
| 60 | 98.4 | | 1.4 | | | |
| | Amount of Acetaminophen Dissolved | | | | | |
| 15 | 94.0 | | 5.1 | | | |
| 30 | 97.0 | | 1.5 | | | |
| 45 | 98.1 | | 1.4 | | | |
| 60 | 98.6 | | 1.4 | | | |

Comments:

1. The test drug is rated AA in the Orange Book, it is in conventional dosage form and does not present bioequivalence problems.
2. The dissolution method and results comply with those published in USP 23 with the tolerance of "not less than of each of the labeled amounts of acetaminophen and oxycodone HCl are dissolved in 45 minutes".

Recommendation:

1. The Division of Bioequivalence agrees that the information submitted by Endo Pharmaceuticals Inc. demonstrates that its oxycodone hydrochloride/acetaminophen tablets, 2.5 mg/325 mg and 5 mg/325 mg, fall under 21 CFR Section 320.22(c) of the Bioavailability/Bioequivalence Regulations. Waiver requests of *in vivo* bioequivalence study for test products are granted.
2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1 N HCl, using USP XXIII apparatus II (Paddle) at 50 rpm. The test product should meet the following revised specifications:

Not less than _____ of the labeled amount of
both acetaminophen and oxycodone hydrochloride
are dissolved in 45 minutes.

Lin-Whei Chuang 11/5/98

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

Y et al - f 11/6/98

Concured *Dale R. Conner* Date: 11/9/98
Dale Conner, Pharm. D.
Director, Division of Bioequivalence

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

40-330

APPLICATION NUMBER:

CORRESPONDENCE



Endo Pharmaceuticals Inc.

May 6, 1999

VIA FACSIMILE

Douglas Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA ORIG AMENDMENT

N/FA

Re: ANDA 40-330; Oxycodone and Acetaminophen Tablets, USP
2.5 mg/325 mg and 5 mg/325 mg
Telephone Amendment

Dear Mr. Sporn:

Reference is made to yesterday's conversation with Mr. Glen Smith, Review Chemist, OGD in regards to the subject drug product.

Mr. Smith commented on the assay stability data of the 9 month test point for the blister package and was interested to know if the assay data at the 12 month test point had increased or leveled off. I indicated to Mr. Smith that the oxycodone assay data at 12 months had leveled off as follows:

| Strengths | 9 month (oxycodone assay) | 12 month (oxycodone assay) |
|-------------|------------------------------|-------------------------------|
| 2.5mg/325mg | 96.8% | 96.8% |
| 5.0mg/325mg | 95.3% | 96.6% |

As requested, we are enclosing the 12 month stability data on the blister package for both strengths, 2.5 mg/325 mg and 5 mg/325 mg.

This letter is being faxed today to Mr. Smith and a hard copy will follow.

If there are any further questions, please contact me at (516) 522-3305.

Sincerely,

Carol Patterson, MS
Manager, Regulatory Affairs

attachments
CAP:wj
FDA-1999.doc

RECEIVED

MAY 07 1999

GENERIC DRUGS



FACSIMILE AMENDMENT

Endo Pharmaceuticals Inc.

April 19, 1999

Douglas Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

**Re: ANDA 40-330; Oxycodone and Acetaminophen Tablets, USP
2.5 mg/325 mg and 5 mg/325 mg
CMC Response to April 12, 1999 Deficiency Letter**

Dear Mr. Sporn:

Reference is made to the attached facsimile letter which contains both labeling, and CMC (chemistry, manufacturing and controls) comments on the original application dated August 28, 1998 for the subject product.

We are amending this application with our responses to the CMC comments. As per my conversation with Mr. Adolph Vezza in the Labeling Division, we will submit a response to the labeling comments and provide final printed labeling under a separate cover. The electronic submission for this paper amendment will also be submitted along with the labeling response.

Included in this amendment are the following:

- Completed FDA Form 356h
- Field Copy Certification
- A copy of FDA's April 12, 1999 Facsimile Deficiency Letter
- CMC Responses

The following is our understanding of the status of the review of this application:

RECEIVED

APR 20 1999

Pre-Approval Inspection for:

- Manufacturing facility, was
waived in a letter dated October 21, 1998.
- Blister Packaging Facility,
began April 7, 1999.
- Blister Packaging Facility, New Jersey
- OGD is awaiting evaluation from Compliance Division.

Bioequivalence: The attached FDA letter (April 12, 1999), indicates that the review has been completed with no further comments.

Methods Validation: As per Mr. Tim Ames, Project Manager, Office of Generic Drugs, Methods Validation is not necessary since the product is USP.

CMC: The response to the April 12, 1999 facsimile deficiency letter is enclosed in this amendment.

Labeling: Comments were received in the April 12, 1999 facsimile deficiency letter and the responses will be submitted under separate cover.

If there are any questions regarding this amendment or any further open issues on this application, please contact me at (516) 522-3305.

Sincerely,



Carol A. Patterson, MS
Manager, Regulatory Affairs

attachments

CAP:wj
Def. Response/OxyAPAP 4-12-99

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-330 APPLICANT: Endo Pharmaceuticals
DRUG PRODUCT: Oxycodone and Acetaminophen Tablets USP
2.5 mg/325 mg, 5.0 mg/325 mg

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. The amount of Microcrystalline Cellulose shown in your composition statement should not be considered accurate since it will always be reduced by a significant amount when you compensate for the amount of contained in . Please revise your composition statements to more accurately reflect the amount of Microcrystalline Cellulose prior to compensating for the assay value of instead of the assay value of . n
2. The USP <671> Container Permeation testing results for the 500 cc bottle were indicated as In-Progress. Please submit final test results.
3. Your blend uniformity specification failed to include an RSD limit and indicated that testing would only occur for the first three validation batches. Please revise their specifications to include a RSD value of 5.0% and indicate testing of all commercial batches.
4. Please revise your in-process tablet weight specification to include individual tablet weight specifications.
5. As noted in your application, the Oxycodone values appeared to decrease during the accelerated stability testing in the blister packaging. While the values remained within specifications, please submit all room temperature stability data accrued to date to support your proposed expiry dating of 24 months.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

We note that you have submitted alternate analytical methods to be used in the testing of drug substance and/or drug product. Please be advised that approval to use an analytical procedure that differs from that in the USP does not release your firm from any obligations to comply with the methods and procedures in the USP. You should be aware that USP procedures remain the regulatory method, and results obtained thereof will rule in the event of a dispute.

Sincerely yours,

M Smela for

Florence Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY -COMMENTS

ANDA: 40-330

APPLICANT: Endo Pharmaceuticals Inc.

DRUG PRODUCT: Oxycodone Hydrochloride & Acetaminophen
Tablets (2.5 mg/325 mg & 5 mg/325 mg)

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Paul F. Conner

Dale Conner, Pharm. D.
Director, Division of
Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and
Research



Endo Pharmaceuticals Inc.

CMC ESD
BA/BE ESD

October 5, 1998

ANDA ORIG AMENDMENT
AA

Douglas Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

RECEIVED

OCT 06 1998

GENERIC DRUGS

Re: **ELECTRONIC SUBMISSION (CMC & BA/BE)**
Oxycodone and Acetaminophen Tablets, USP
2.5 mg/325 mg and 5 mg/ 325 mg

40-330

Dear Mr. Sporn:

Reference is made to our Original Abbreviated New Drug Application submitted August 24, 1998 for the above-referenced drug product.

We are submitting herein the Electronic Submission Documents (ESD) for the chemistry, manufacturing and controls information and the bioequivalence section of the ANDA in accordance with the 45-day grace period allowed by OGD during the CMC ramp-up implementation period.

Enclosed in this submission are four (4) diskettes containing the CMC and BA/BE Electronic Submissions, each in duplicate. The CMC submission consists of the electronic submission document (ESD), the EVA export log file, and the CMC companion document. The Bioequivalence submission files include the BA/BE ESD, the EVA export log file, and the BA/BE companion document.

Our application for this drug product includes a request for waiver of *in-vivo* bioequivalence studies (biowaiver) for both strengths. We have prepared the applicable portions of the electronic submission for Bioequivalence to reflect the product information and dissolution data supporting the biowaiver, in order to help test the ability of the system to handle this situation (as discussed with Richard Sponaule during training at the University of Maryland).

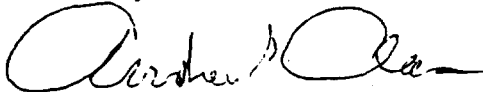
Please note that Michele Ritondo, Ph.D., GloboMax, L.L.C., provided consultative assistance in preparing this submission.

We hereby declare that, to the best of our knowledge, the information contained in this electronic submission is the same as the August 24, 1998 paper submission. The presentation of the information may differ in order to conform to the ESD/EVA template. For example, for the Manufacturing Process Step form, the manufacturing steps for the blank and executed batch records have been organized into seven major steps, consistent with the Process Flow Diagram (see page 348 of the original ANDA).

Endo Pharmaceuticals Inc. is very pleased to participate in OGD's electronic submissions initiative for the CMC and bioequivalence sections of the ANDA. During the preparation of this electronic submission, we provided our comments and observations to the instructors and project developers at the University of Maryland, as well as receiving their helpful advice. We would also appreciate your feedback regarding this submission.

If there are any questions or comments, please contact me at (516) 522-3309.

Sincerely,

A handwritten signature in black ink, appearing to read "Andrew G. Clair".

Andrew G. Clair, Ph.D.
Director, Regulatory Affairs

enclosures

AGC:wj
FDA-1998.doc(conf d)

BIOEQUIVALENCY COMMENTS

ANDA: 40-330 APPLICANT: Endo Pharmaceuticals Inc.

DRUG PRODUCT: Oxycodone Hydrochloride & Acetaminophen
 Tablets (2.5 mg/325 mg & 5 mg/325 mg)

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale Conner, Pharm. D.
Director, Division of
Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and
Research

Should you have questions concerning this application, contact:

Sincerely yours,

Endorsement: HFD-615/PRickman, Chief, RSB Whelan date 10/2/98
HFD-615/SMiddleton, CSO, Jacinda J. M. Middleton date 9/15/98
HFD-647/UVenkataram, Sup. Chem. _____ date _____
WP File x:\new\firmam\endo\ltrs&rev\40330.ack
FT/mjl/9/14/98
ANDA Acknowledgment Letter!

Endo Pharmaceuticals Inc.
Attention: Andrew G. Clair, Ph.D.
500 Endo Blvd.
Garden City, NY 11530
|||

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

DATE OF APPLICATION: August 24, 1998

We will correspond with you further after we have had the opportunity to review the application.

In addition, we recommend that you use the updated form 356h instead of the expired FDA form 3439. A revised copy of this form can be found on the following Internet site:

<http://aosweb.psc.dhhs.gov/forms/fdaforms.htm>



Endo Pharmaceuticals Inc.

August 24, 1998

*Check file in
9/10/98
J. M. McCallister*

Douglas Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

**Re: Original Abbreviated New Drug Application
Oxycodone and Acetaminophen Tablets, USP
2.5 mg/325 mg and 5 mg/325 mg**

Dear Mr. Sporn:

Pursuant to 21 CFR 314.94 and Section 505(j) of the Federal Food, Drug and Cosmetic Act, Endo Pharmaceuticals Inc. ("Endo") hereby submits this original Abbreviated New Drug Application for the above referenced Oxycodone and Acetaminophen Tablets, both of which will be branded as Percocet®: 2.5 mg/325 mg tablets (pink) and a reformulated version of the currently approved strength of Percocet®, 5 mg/325 mg tablets which will be blue in color. Both of the new products which are the subject of this application are manufactured by a process.

The reference listed drug product is Endo's current Percocet® Tablets, 5 mg/325 mg, (ANDA 85-106), a white tablet manufactured via a process. This same product is also marketed by Endo under the name Endocet®.

A new tablet strength proposed in this ANDA, Oxycodone and Acetaminophen 2.5 mg/325 mg (a pink tablet), was found suitable for submission as an ANDA via approval by the Agency of an ANDA suitability petition (Petition Doc. No. 97P-0347/CPI) based on the current Percocet® Tablet, (oxycodone and acetaminophen), 5 mg/325 mg. A copy of the suitability petition approval letter is enclosed in Section II - "Basis for ANDA Submission".

The second strength in this proposed ANDA, the 5 mg/325 mg blue tablet is a reformulation of the currently approved Percocet® 5 mg/325 mg white tablet which is manufactured for Endo by ~~in~~ **Manati, Puerto Rico**. The proposed new product will be manufactured for Endo by **Manati, Puerto Rico**.

Because the manufacturing processes are different and because

AUG 25 1998

Endo wishes to retain both processes and manufacturing sites at this time (we will continue to distribute and market a white oxycodone/acetaminophen 5 mg/325 mg tablet manufactured by the v process as Endocet®), a separate ANDA is being filed, since only one manufacturing process can be included in a single ANDA.

Upon approval of the Percocet® blue 5 mg/325 mg tablet, distribution and marketing of the current Percocet® white 5 mg/325 mg tablet will be discontinued. The white Endocet® 5 mg/325 mg tablet will then be the only product marketed under ANDA 85-106. A supplement to ANDA 85-106 will be filed to withdraw the brand name Percocet® from ANDA 85-106 held for 1 process, effective on the date this new ANDA is approved.

To avoid any market confusion at the time of launch we commit to doing a 6 month stickering program for the blue Percocet® to alert health care providers of the new blue color of Percocet® 5 mg/325 mg tablet.

Based on the "AA" rating of the reference-listed drug, Percocet® Tablets in the Orange Book and on prior conversations with the FDA, we are requesting a waiver of the need to demonstrate in-vivo bioequivalence between the formulations that are the subject of this proposed ANDA and the reference-listed drug. To support this request for a waiver, we have enclosed in Volume 1.4, comparative *in-vitro* dissolution data of the proposed products compared to the reference product in accordance with OGD's requirement.

We have discussed the general filing concept with the members of your staff. Prior correspondence between FDA and Endo Pharmaceuticals Inc. is referenced in Section XXI.

This ANDA consists of four volumes, Volume 1.1 to 1.4 submitted in duplicate, an archival copy (blue binders) and a technical review copy (red binders). Volumes 1.1 to 1.3 are the CMC volumes and Volume 1.4 is the bioequivalence volume. Duplicate copies of the Methods Validation Package are submitted in black binders. The field copy certification letter is enclosed.

The following information is provided for clarification during the review:

- Name of Drug Product

There were several names included in the submitted documentation that were used interchangeably during the development of the formulations that are the subject of the proposed ANDA. These names are synonymous and they are: EN3200, Percocet® Variant, Percocet®, and Oxycodone and Acetaminophen Tablets.

- Company Name Changes

Endo Pharmaceuticals Inc. is an independent, fully integrated pharmaceutical company that was formed as a result of a management buy-out from The DuPont Merck Pharmaceutical Company. The Management buy-out which concluded in August 1997 included the acquisition by Endo Pharmaceuticals Inc. of DuPont Merck's wholly owned generic subsidiary, Endo® Laboratories, L.L.C. and several other products and assets.

On July 1, 1998, the joint venture between DuPont and Merck which created The DuPont Merck Pharmaceutical Company came to an end with the formal dissolution of the joint venture entity. As such, the old DuPont Merck entity is now incorporated into the DuPont Pharmaceuticals Company, part of DuPont Life Sciences Enterprise.

Notification of Electronic Submission

We will be filing an electronic submission for this ANDA within 45 days of the filing of the paper ANDA in accordance with the guidelines issued by the Office of Generic Drugs.

Endo Pharmaceuticals Inc. hereby declare that to the best of our knowledge, the data contained in the electronic submission will be the same as in this paper submission unless otherwise noted.

Please be advised that the materials and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under the application provision 18 U.S.C. Section 331(j).

Any question³ regarding this application may be directed to me at (516) 522-3305. Any written communications may be faxed to me at (516) 832-2291.

Sincerely



Carol Patterson, M.S.
Manager, Regulatory Affairs.

attachments

CAP:wj
FDA-1998.doc